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Massive Urinary Protein Excretion Associated with Greater Neonatal Risk in Preeclampsia

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Abstract

Objective The objective of this study was to compare clinical outcomes of preeclamptic pregnancies according to the proteinuria level.

Study Design Secondary analysis of a multicenter prospective cohort study of women with preeclampsia (PE) symptomatology. Nonproteinuria, mild-proteinuria, and massive-proteinuria PEs were defined as: < 165 mg in 12 hours or < 300 mg in 24 hours, 165 mg to 2.69 g in 12 hours or 300 mg to 4.99 g in 24 hours, and ≥ 2.7 g in 12 hours or ≥ 5.0 g in 24 hours, respectively. Individual and composite maternal, fetal, and neonatal outcomes were compared among the PE groups.

Results Of the 406 analyzed pregnancies, 36 (8.8%) had massive-proteinuria PE, 268 (66.0%) mild-proteinuria PE, and 102 (25.1%) nonproteinuria PE. Compared with the other groups, massive-proteinuria PE women had significantly higher blood pressures ($p < 0.001$), epigastric pain ($p = 0.007$), and uric acid serum levels ($p < 0.001$) prior to delivery. Composite maternal morbidity was similar across the groups. Delivery $< 34^{0/7}$ weeks occurred in 80.6, 49.3, and 22.5% of massive-proteinuria, mild-proteinuria, and nonproteinuria PE groups, respectively ($p < 0.0001$). Composite adverse neonatal outcomes were significantly higher in the massive-proteinuria PE compared with the other groups ($p = 0.001$).

Conclusion While potentially not important diagnostically, massive proteinuria is associated with more severe clinical manifestations of PE prompting earlier delivery.

Keywords
- proteinuria
- PETRA study
- preeclampsia
- complications
- preterm delivery

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Preeclampsia (PE) affects approximately 3 to 5% of the pregnant population and is a leading cause of maternal and perinatal morbidity and mortality.[1] One-quarter of medically indicated preterm deliveries are linked to PE.[2] In the past decades, a progressively increasing prevalence of PE has been attributed to multiple risk factors including a significant rise in maternal obesity and diabetes,[3–5] delayed childbearing and to an increased rate of multiple gestations.[6] Women who develop PE are at significant risk of early cardiovascular disease, hypertension, cerebrovascular accidents, and death.[7–9] Furthermore, there is growing evidence that offspring born to preeclamptic women are at increased risk for early onset of cardiovascular disease and stroke during adulthood.[10,11] That risk seems to be more substantial when PE is diagnosed before 34 weeks of gestation.[11]

In 2002, the American College of Obstetricians and Gynecologists (ACOG) practice bulletin[12] recommended following the diagnostic criteria of PE established by the National High Blood Pressure Education Program Working Group in 2000.[13] This group defined PE as new onset of hypertension: systolic blood pressure (SBP) $\geq$ 140 mm Hg or diastolic BP (DBP) $\geq$ 90 mm Hg after 20 weeks in a previously normotensive woman and proteinuria along with a protein excretion of $\geq$ 0.3 g in a 24-hour period.[13] Women with proteinuria $\geq$ 5 g in a 24-hour specimen or $\geq$ 3+ on two random urine samples collected at least 4 hours apart met criteria for severe disease by the 2002 ACOG criteria.[12] In 2013, ACOG published new recommendations on hypertension in pregnancy elaborated by a multidisciplinary panel of experts.[14] Important changes to the PE definition were made including elimination of the severe PE diagnosis in pregnancies with gestational hypertension and a proteinuria level of $\geq$ 5 g in 24 hours.[14] The rationale behind this new definition was convincing evidence demonstrating a lack of association between the level of urinary protein (UP) loss and pregnancy outcomes.[14] According to ACOG, the amount of proteinuria or change in the amount of proteinuria, as isolated factors, does not justify delivery in preeclamptic pregnancies with a gestational age (GA) $< 37^{0/7}$ weeks.[14]

In the new criteria, ACOG recommends diagnosing PE in the absence of proteinuria when any of several abnormalities are present: thrombocytopenia (platelet count $<$ 100,000/μL), elevated levels of liver transaminases twice or more above the normal concentrations, elevated serum creatinine $>$ 1.1 mg/dL or a doubling elevation in absence of other renal disease, pulmonary edema, or new-onset cerebral or visual disturbances.[14] Furthermore, "severe features of PE" is diagnosed when any of these findings are present or when maternal SBP is $\geq$ 160 mm Hg or DBP $\geq$ 110 mm Hg on two occasions at least 4 hours apart while the patient is on bed rest.[14] Maternal/fetal conditions and GA are the most important factors in determining the timing of delivery of women with severe disease. For those pregnancies with stable maternal and fetal conditions and GA $< 34^{0/7}$ weeks, expectant management that involves daily maternal and fetal surveillance is recommended at medical centers equipped with adequate maternal and neonatal intensive care resources.[14]

The relationship between heavy proteinuria and adverse clinical events in pregnancies complicated by PE has been investigated in multiple studies.[15–23] Some studies have shown that the level of proteinuria is not associated with adverse maternal[15–18,20] or perinatal outcomes.[15–20] However, others have reported that heavy proteinuria increases both maternal and perinatal morbidities including severe hypertension, preterm delivery, cesarean delivery, small for GA (SGA) infants, maternal symptoms, and perinatal mortality rate.[21–25] These conflicting results likely reflect limitations of previous studies including retrospective design,[15] proteinuria quantification by qualitative dipstick method,[16–18] performance in single-care settings,[17,22,23] and inclusion of hypertensive disorders other than PE to examine pregnancy outcomes.[19] Given the recent revision of the diagnostic criteria for PE, we believe it is appropriate to reconsider the association between the degree of proteinuria with the clinical course and pregnancy outcome of PE.

PE Triage by Rapid Assay (PETRA) of novel biomarkers of placental function and maternal adaptation was a recent multicenter prospective cohort study that enrolled women with any signs or symptoms of PE. The primary objective of this study was to validate the Triage placental growth factor test as an aid in the diagnosis of PE in symptomatic women. Importantly, this study classified PE using the most recent ACOG's clinical criteria. The final diagnosis was adjudicated by a panel of independent experts allowing us to compare pregnancy outcomes between nonproteinuric and proteinuric PEs. The objective of our study was to determine whether preeclamptic pregnancies with massive proteinuria, defined as $>$ 2.7 g in 12 hours or $>$ 5.0 g in 24 hours, have worse maternal, fetal, or neonatal outcomes compared with those with mild or nonproteinuria.

Materials and Methods

We conducted a secondary analysis of the multicenter PETRA prospective cohort study. In PETRA, pregnant women 16 to 45 years of age at $20^{0/7}$ to $40^{0/7}$ weeks of gestation with signs or symptoms of PE were enrolled at 24 centers in the United States and Canada between June 2010 and July 2012. Patients were excluded if the pregnancy had more than three viable fetuses, active substance abuse, were on dialysis, received blood product transfusion within the previous 48 hours, had known or suspected infection with human immunodeficiency virus, hepatitis C virus, hepatitis B virus, or other infectious hepatitis. We also excluded women with underlying renal disease. This study was approved by the Institutional Review Board at our institution.

Signs or symptoms of PE that warranted initial evaluation were new onset of hypertension defined as SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg or rise of SBP $\geq$ 30 mm Hg or DBP $\geq$ 15 mm Hg from patient's BP baseline; worsening BP in patients with chronic hypertension; proteinuria defined as $\geq$ 1+ dipstick, $\geq$ 0.30 UP/creatinine ratio (UP/CR), or $\geq$ 300 mg in 24 hours. Symptoms potentially associated with PE included persistent epigastric or right upper abdominal pain, nausea, vomiting, or headaches/visual

disturbances; excessive weight gain $\geq$ 5 pounds per week; laboratory abnormalities such as thrombocytopenia (platelets $<$ 100,000/μL), aspartate aminotransferase (AST), and alanine transaminase (ALT) twice normal, serum creatinine $>$ 1.1 mg/dL or having doubled, uric acid $>$ 6.0 mg/dL; unexplained clinical events including oliguria, pulmonary edema, and seizure; fetal growth restriction defined as sonographic estimated fetal weight (EFW) $\leq$ 10th percentile for GA; and suspected fetal/placental hydrops, uterine artery Doppler notching, or placental abruption.

At enrollment, demographic and baseline characteristics such as maternal age, gravity and parity, race, $\geq$ 30 kg/m^2 body mass index, PE in previous pregnancies, history of lupus, history of antiphospholipid antibody syndrome, and smoking status were recorded. GA was assigned by a certain regular last menstrual period (LMP) confirmed by the earliest ultrasound exam. Estimated date of confinement (EDC) was assigned by the earliest ultrasound in women with irregular menstrual cycles or an uncertain LMP. The earliest ultrasound instead of LMP was used for EDC assignment if discrepancies existed as: $\pm$ 5 days for a first trimester (6^0–13^6 weeks) ultrasound, $\pm$ 10 days for an early second trimester (14^0–22^6) ultrasound, $\pm$ 14 days for a late second trimester (23^0–27^6) ultrasound, and $\pm$ 21 days for a third trimester (28^0 to term) ultrasound. BP was obtained following ACOG's recommendations.[12] Laboratory evaluations included hematocrit, platelet count, serum creatinine, ALT, AST, lactate dehydrogenase (LDH), and uric acid. Women with proteinuria $\geq$ 1+ on dipstick or UP/CR $\geq$ 0.3 mg/mg underwent 12-hour or 24-hour urine protein excretion assessment. Patients without criteria for PE at the initial study visit whose diagnosis was again suspected at least 1 week later underwent re-evaluation in the same fashion. Medical management including hospitalization, expectant management, and delivery was determined by the attending physicians and internal protocols of the participating institutions.

Our cohort consisted of women with diagnosis of PE adjudicated by an independent expert panel following the most recent guidelines.[14] HELLP syndrome was defined as PE plus AST and ALT twice normal, LDH twice normal, and thrombocytopenia (platelets $<$ 100,000/μL). Preeclamptic pregnancies were classified in three groups according to the degree of proteinuria: (1) nonproteinuria PE was defined as either proteinuria $<$ 165 mg in 12 hours or $<$ 300 mg in 24 hours; (2) mild-proteinuria PE included patients with proteinuria between 165 mg and 2.7 g in 12 hours or from 300 mg to 4.9 g in 24 hours; and (3) massive-proteinuria PE criteria were proteinuria $>$ 2.7 g in 12 hours or $>$ 5.0 g in 24 hours. We used 12 hours proteinuria cutoff values that have been reported to correlate well with 24 hours urine proteinuria values in previous studies.[26,27] The highest timed proteinuria value was selected in cases with multiple testing. Maternal demographic and clinical characteristics were compared between the PE groups. BP values, symptomatology, and laboratory parameters within 24 hours of delivery were analyzed in each group. Mode of delivery, timing of delivery, birth weight, Apgar scores, and arterial cord gas values were also analyzed when available. Women with superimposed PE were excluded.

Maternal, fetal, and neonatal outcomes were compared among the PE subgroups categorized by their degree of proteinuria. Composite adverse maternal outcome was defined as the presence of any of the following: acute renal failure, liver hematoma/rupture, acute myocardial infarction, cortical blindness, retinal detachment, cerebrovascular accident, pulmonary edema/adult respiratory distress syndrome, placental abruption, eclampsia, need for third intravenous agent to control BP, disseminated intravascular coagulation, or maternal death. Composite adverse fetal outcome included preterm delivery $< 34^{0/7}$ weeks or $< 37^{0/7}$ weeks, intrauterine growth restriction (IUGR) defined as EFW $<$ 10th percentile or $<$ 5th percentile by ultrasound exam, or antepartum/intrapartum fetal death. Composite adverse neonatal outcome was defined as any of the following: respiratory distress syndrome (RDS), any grade of intraventricular hemorrhage (IVH), necrotizing enterocolitis, bronchopulmonary dysplasia, periventricular leukomalacia, retinopathy of prematurity, seizure, or neonatal intensive care unit (NICU) admission for $>$ 48 hours for full-term infant. Diagnosis of neonatal complications was made by the neonatologists at individual participating sites following institutional standardized protocols. Chi-square test was used for analysis of categorical variables and analysis of variance (ANOVA) was used to compare continuous data. Fisher's exact test was used when cells had expected counts less than 5. The Wilcoxon rank-sum test was used to analyze differences in the median GA at diagnosis of PE. Post hoc Tukey's test was performed after ANOVA when indicated. Level of significance was set at $<$ 0.05. All reported tests of statistical significance were two sided. All analyses were performed with SAS for Windows (version 9.4).

Results

A total of 675 patients were adjudicated with a final diagnosis of PE by the PETRA's independent panel. Of these, 406 women (60.1%) underwent timed 12 or 24 hours urine collections. One-hundred two women (25.1%) were classified as nonproteinuria PE, 268 pregnancies (66.0%) had mild-proteinuria PE, and 36 cases (8.8%) had massive-proteinuria PE. Baseline demographic and clinical characteristics were similar among the three groups, with the exception of nulliparity which was more prevalent in women with massive-proteinuria PE (►**Table 1**). The rate of twin and triplet gestations was low and not significantly different between the PE groups. Mean UP excretion levels in each group are depicted in ►**Table 1**. Massive-proteinuria PE women compared with mild-proteinuria and nonproteinuria PE groups were enrolled at a much earlier GA (median GA = 30.6 weeks [interquartile range, IQR, 28.2–33.6] vs. 32.4 weeks [IQR, 28.2–33.6] and 32.9 weeks [IQR, 30.4–35.6], respectively, ►**Table 1**; $p = 0.002$). Mean SBP and DBP within 24 hours of delivery was significantly higher in mass-proteinuria PE pregnancies compared with those with mild and no proteinuria ($p < 0.001$; ►**Table 1**).

Table 1 Demographic and clinical characteristics of women with PE stratified by protein quantity in urine

	Nonproteinuria		Mild proteinuria		Massive proteinuria		*p*-Value
	N = 102	%	*N* = 268	%	*N* = 36	%	
Plurality							
Singletons	96		245		32		0.82
Multiples	6		23		4		
Twins	5		20		2		
Triplets	1		3		2		
Age (y)							
16–24	28	27.5	90	33.6	13	36.1	0.76
25–34	54	52.9	130	48.5	18	50.0	
35–45	20	19.6	48	17.9	5	13.9	
Gravidity							
Nulliparous	53	52.0	168	62.7	29	80.6	0.003
Multiparous	49	48.0	100	37.3	7	19.4	
Race							
White	58	56.9	147	54.9	23	63.9	0.70
Black	30	29.4	87	32.5	7	19.4	
Asian	3	2.9	5	1.9	1	2.8	
Other	11	10.8	29	10.8	5	13.9	
Median GA at enrollment (wk; IQR)	32.9 (30.4–35.6)		32.4 (29.7–34.9)		30.6 (28.2–33.6)		0.002[a]
BMI $\geq$ 30	63	61.8	169	63.1	21	58.3	0.94
Tobacco use							
Present	79	77.5	227	84.7	28	77.8	0.18
Quit	23	22.5	41	15.3	8	22.2	
H/O preexisting diabetes	9	8.8	14	5.2	2	5.6	0.75
H/O lupus	0	0	2	0.7	1	2.8	0.38
H/O APS	0	0	1	0.4	0	0	0.26
H/O PE in a previous gestation	37	36.3	77	28.7	7	19.4	0.26
Mean SBP[b] (mean $\pm$ SD)	143.3 $\pm$ 12.1		145.7 $\pm$ 11.6		148.3 $\pm$ 8.9		$<$ 0.001[a]
Mean DBP[b] (mean $\pm$ SD)	84.2 $\pm$ 8.8		86.7 $\pm$ 7.8		88.6 $\pm$ 8.0		$<$ 0.001[a]
Highest SBP[c] (mean $\pm$ SD)	168.1 $\pm$ 20.7		171.5 $\pm$ 18.2		175.4 $\pm$ 16.1		0.0008[d]
Highest DBP[c] (mean $\pm$ SD)	101.9 $\pm$ 13.5		103.4 $\pm$ 10.9		108.3 $\pm$ 16.7		0.006[a]
24-h proteinuria (mg; mean $\pm$ SD)	162.9 $\pm$ 74.5		1,170 $\pm$ 1,149		9,117 $\pm$ 4,722		0.0001[e]
12-h proteinuria (mg; mean $\pm$ SD)	117.0 $\pm$ 41.0		793.9 $\pm$ 734.7		6,015 $\pm$ 976.6		0.0001[d]

Abbreviations: APS, antiphospholipid antibody syndrome; BMI, body mass index early in gestation; DBP, diastolic blood pressure; GA, gestational age; H/O, history of; IQR, interquartile range; PE, preeclampsia; SBP, systolic blood pressure; SD, standard deviation.
[a]Significant difference between massive-proteinuria PE and the other PE groups.
[b]Mean blood pressures within 24 hours before delivery.
[c]Highest blood pressure before delivery.
[d]Significant difference between non-proteinuria PE and the other PE groups.
[e]Significant difference in all multiple comparisons between the PE groups.

Platelet count and liver enzymes serum levels were similar among the groups. The uric acid levels were higher in the massive-proteinuria PE (median, 6.7 mg/dL; IQR, 5.5–7.6) compared with the mild-proteinuria PE (median, 5.9 mg/dL; IQR, 4.9–7.0) and nonproteinuria PE (median, 5.1 mg/dL; IQR, 4.3–5.8) groups ($p < 0.001$; ►**Table 2**). Uric acid was also significantly higher in the mild-proteinuria PE compared with nonproteinuria PE pregnancies. Among clinical signs and symptoms related to PE (►**Table 3**), RUQ/epigastric pain was reported in 19.4% of massive-proteinuria PE women

Table 2 Laboratory parameters within 24 hours of delivery in the PE subgroups

	Nonproteinuria		Mild proteinuria		Massive proteinuria		*p*-Value
	N = 102	Median (IQR)	*N* = 268	Median (IQR)	*N* = 36	Median (IQR)	
Platelets (N/μL)	95	207.0 (160.0–258.0)	223	202.0 (161.0–246.0)	33	196.0 (153.0–228.0)	0.33
AST (U/L)	87	21.0 (17.0–32.0)	210	21.0 (17.0–31.0)	31	24.0 (20.0–34.0)	0.16
ALT (U/L)	86	16.0 (12.0–27.0)	205	17.0 (12.0–28.0)	31	18.0 (14.0–34.0)	0.54
Serum creatinine (mg/dL)	86	0.6 (0.5–0.7)	210	0.6 (0.5–0.7)	34	0.7 (0.6–0.8)	< 0.01[a]
Uric acid (mg/dL)	62	5.1 (4.3–5.8)	154	5.9 (4.9–7.0)	22	6.7 (5.5–7.6)	< 0.001[b]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; PE, preeclampsia.
[a]Significant difference between massive-proteinuria PE compared with mild-proteinuria PE and nonproteinuria PE.
[b]Significant difference in all multiple comparisons between the groups.

compared with 5.2% in mild-proteinuria PE and 7.8% of nonproteinuria PE patients ($p = 0.007$; significant difference between mild- and massive-proteinuria PEs). Maternal neurological symptoms did not vary significantly between the PE subgroups. HELLP syndrome was diagnosed in 2/36 (5.6%) of massive-proteinuria PE, in 1/268 (0.4%) of mild-proteinuria PE, and in 4/102 (3.9%) of those with nonproteinuria PE. HELLP syndrome rate was significantly lower in the mild-proteinuria PE group compared with the other groups ($p < 0.005$), but similar between nonproteinuria and massive-proteinuria PEs.

There was not a significant difference in either individual or composite adverse maternal morbidity among the PE groups (►**Table 4**). Adverse maternal morbidity was uncommon overall, with any element occurring in < 6% of cases in all three groups. There were no cases of maternal death. Median GA (IQR) at delivery for massive-proteinuria, mild-proteinuria, and nonproteinuria PE groups were 31.3 (28.6–33.6), 34.0 (30.6–36.7), and 36.6 (34.1–38.4) weeks, respectively (►**Table 5**; $p < 0.001$). Preterm delivery < $34^{0/7}$ weeks occurred in 80.6% of massive-proteinuria PE patients, in 49.3% of mild-proteinuria PE women, and in 22.5% of women with nonproteinuria PE ($p < 0.0001$). The difference in the preterm birth rate < $34^{0/7}$ weeks between the nonproteinuria and mild-proteinuria PE groups was also significant ($p < 0.0001$). Similar differences were noted in the delivery rate < $37^{0/7}$ weeks across all the groups (►**Table 5**). Cesarean delivery rate was significantly higher in the massive-proteinuria PE (86.1%) than in the mild-proteinuria PE (64.9%) and nonproteinuria PE (55.9%) groups ($p = 0.0001$). Stillbirth and IUGR (both, EFW < 10th percentile or EFW < 5th percentile by ultrasound exam) rates were similar across the groups (►**Table 5**). Composite adverse fetal outcome was driven by the significant differences noted in the preterm delivery rates among the groups, with the highest percentages noted, as mentioned earlier, in the massive-proteinuria PE group.

Of our study's 443 neonates, 42 (9.4%) were born to massive-proteinuria, 292 (66.0%) to mild-proteinuria, and 109 (24.6%) to nonproteinuria PE women. Mean birth weight was significantly lower in the massive-proteinuria PE neonates (1,392 ± 557 g) compared with those born to mild-proteinuria PE (1,937 ± 892 g) and nonproteinuria (2,456 ± 885 g) PE women ($p < 0.001$). The differences in birth weight were also significant between nonproteinuria and mild-proteinuria PE neonates (►**Table 6**). Apgar score < 7 at 5 minutes was reported more commonly in the massive-proteinuria PE infants (19.0%) than for mild-proteinuria (7.2%) and nonproteinuria (6.4%) groups, respectively ($p = 0.0005$). Umbilical arterial cord gasses were reported only in 226 of 443 subjects (51.0%) and there was no difference on the mean pH or in the number of pH values < 7.0 across the groups. RDS was the most common neonatal complication affecting 47.6% of massive-proteinuria PE, 28.8% of mild-proteinuria PE, and 11.0% of non-proteinuria

Table 3 PE-related symptoms between the PE subgroups

	Nonproteinuria		Mild proteinuria		Massive proteinuria		*p*-Value
	N = 102	%	*N* = 268	%	*N* = 36	%	
RUQ pain/epigastric pain	8	7.8	14	5.2	7	19.4	0.007[a]
Headache, visual changes	34	33.3	104	38.8	16	44.4	0.79
Nausea and vomiting	8	7.8	25	9.3	6	16.7	0.29

Abbreviations: PE, preeclampsia; RUQ, right upper quadrant.
[a]Significant difference between massive-proteinuria and mild-proteinuria PE groups.

Table 4 Individual and composite adverse maternal outcome in women with PE stratified by protein quantity in urine

	Nonproteinuria		Mild proteinuria		Massive proteinuria		*p*-Value
	N = 102	%	*N* = 268	%	*N* = 36	%	
Acute renal failure	0	0	0	0	1	2.8	0.094
Liver hematoma/rupture	0	0	0	0	0	0	N/A
Acute myocardial infarction	0	0	0	0	0	0	N/A
Cortical blindness	0	0	0	0	0	0	N/A
Renal detachment	0	0	0	0	0	0	N/A
Pulmonary edema/ARDS	3	2.9	4	1.5	1	2.8	0.06
Placental abruption	0	0	5	1.9	1	2.8	0.09
Death	0	0	0	0	0	0	N/A
Eclampsia	0	0	0	0	1	2.8	0.09
Third IV antihypertensive agent	1	1.0	8	3.0	0	0	0.11
DIC	0	0	0	0	1	2.8	0.09
Composite adverse maternal outcome	4	3.9	9	3.4	2	5.6	0.70

Abbreviations: ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular disease; IV, intravenous; N/A, not available; PE, preeclampsia.
Note: Fisher's exact tests were used when several cells have expected counts less than 5.

PE newborns ($p < 0.001$; ►**Table 7**). Other individual adverse neonatal outcomes did not differ among the groups. However, composite adverse neonatal outcome, driven mainly by RDS and other prematurity-related complications, was significantly higher in the massive-proteinuria PE than in the other groups ($p = 0.001$; ►**Table 7**). There were no neonatal deaths in any group.

Comment

This prospective cohort study with independent adjudication of PE diagnosis using the new 2013 ACOG criteria indicates that individual and composite adverse maternal outcomes were not increased in preeclamptic women with massive proteinuria compared with those with mild or nonproteinuria PE. However, we found that massive-proteinuria PE was associated with preterm delivery $< 34^{0/7}$ weeks in more than 80% of cases, which was almost twice as high as the mild-proteinuria PE group and almost four times higher than in the nonproteinuria group. Women with massive-proteinuria had more PE-related symptoms and laboratory abnormalities including higher BP, RUQ/epigastric pain, and higher uric acid levels suggesting a more severe clinical presentation. Also, enrollment occurred much earlier in women with massive proteinuria indicating that the diagnosis was made at more preterm GAs. This earlier and more

Table 5 Individual and composite adverse fetal outcomes in women with PE stratified by protein quantity in urine

	Nonproteinuria		Mild proteinuria		Massive proteinuria		*p*-Value
Pregnancies	*N* = 102	%	*N* = 268	%	*N* = 36	%	
Fetuses	*N* = 109	%	*N* = 294	%	*N* = 42	%	
Median GA at delivery (wk; IQR)	36.6 (34.1–38.4)		34.0 (30.6–36.7)		31.3 (28.6–33.6)		< 0.001[a]
Delivery $< 34^{0/7}$ wk	23	22.5	132	49.3	29	80.6	< 0.0001[a]
Delivery $< 37^{0/7}$ wk	66	64.7	190	70.9	31	86.1	0.001[a]
Stillbirth	0	0	2	0.7	0	0	N/A
EFW < 10th percentile	11	10.1	30	10.2	4	9.5	0.99
EFW < 5th percentile	4	3.7	15	5.1	2	4.8	0.83
Composite adverse fetal outcome	64	58.7	228	77.6	40	95.2	< 0.0001[a]

Abbreviations: EFW, estimated fetal weight; GA, gestational age; IQR, interquartile range; PE, preeclampsia.
[a]Significant difference noted in all multiple comparisons between the PE groups.

Table 6 Birth outcomes in PE pregnancies stratified by protein quantity in urine

	Nonproteinuria		Mild proteinuria		Massive proteinuria		*p*-Value
Cesarean delivery, *N* (%)	57 (55.9)		174 (64.9)		31 (86.1)		0.0001[a]
Birth weight (g; mean ± SD)	2,456 ± 885.3		1,937 ± 892.8		1,392 ± 557.0		< 0.001[a]
Neonatal gender	*N*	%	*N*	%	*N*	%	
Female	61	56.0	162	55.5	24	57.1	0.60
Male	48	44.0	130	44.2	18	42.9	
Apgar score < 7 at 5 min	7	6.4	21	7.2	8	19.0	0.0005[b]
Umbilical cord arterial pH < 7.0[c]	1	0.9	1	0.3	0	0	0.40

Abbreviations: GA, gestational age; PE, preeclampsia; SD, standard deviation.
[a]Significant difference in all multiple comparisons between the PE groups.
[b]Significant difference between massive-proteinuria and the other PE groups.
[c]Data available in 226 cases.

severe presentation certainly influenced the clinical management and the final decision for delivery. The higher neonatal morbidity rate seen in infants born to massive-proteinuria women was most likely related to the earlier GA at delivery with RDS being the most common neonatal complication affecting almost half of these infants. The cesarean delivery rate was extremely high (86.1%) in the massive-proteinuria PE group and 19% of newborns from this group had Apgar scores < 7 at 5 minutes. Although we did not analyze fetal testing data, our results suggest the possibility that compromise of the fetal condition played a major role in the mode and timing of delivery in these patients. IUGR, defined as EFW < 10th percentile, occurred in 9.5 to 10.2% of the enrolled pregnancies without significant differences among the groups.

Several studies have shown that the presence of proteinuria in PE increases the risk for specific adverse pregnancy outcomes.[21–25] Using a different proteinuria threshold from our study, a recent secondary analysis of the Vitamins in PE (VIP) trial found that preeclamptic pregnancies with a timed 24-hour proteinuria ≥ 500 mg compared with 300 to 499 mg delivered significantly earlier (33.2 vs. 37.2 weeks) and had a significantly higher cesarean delivery rate (78 vs. 48%).[21] In the VIP trial, preterm delivery < 34 weeks occurred more often in the group with greater proteinuria (26.7 vs. 13.3%). Two prospective cohorts have shown that the presence of proteinuria, defined as UP/CR ≥ 30 mg/mmol,[25] or > 300 mg in 24 hours,[22,25] compared with nonproteinuria in preeclamptic pregnancies is associated with both increased maternal and fetal complications such as hyperuricemia, severe hypertension, renal insufficiency, thrombocytopenia, liver disease, preterm delivery < $37^{0/7}$ weeks, perinatal mortality, and SGA.[22,25] Other investigators have found that elevated UP excretion assessed by spot UP/CR (≥ 0.3 mg/mg) also predisposes to adverse maternal and perinatal outcomes including severe maternal hypertension,

Table 7 Individual and composite adverse neonatal outcome in women with PE stratified by protein quantity in urine

N = 443	Nonproteinuria		Mild proteinuria		Massive proteinuria		*p*-Value
	N = 109	%	*N* = 292	%	*N* = 42	%	
Respiratory distress syndrome	12	11.0	84	28.8	20	47.6	< 0.001[a]
Intraventricular hemorrhage[b]	3	2.8	13	4.5	3	7.1	0.44
Necrotizing enterocolitis	1	0.9	4	1.4	0	0	0.72
Bronchopulmonary dysplasia[b]	0	0	2	0.7	2	4.8	0.10
Periventricular leucomalacia	0	0	0	0	0	0	N/A
Retinopathy of prematurity[b]	2	1.8	7	2.4	4	9.5	0.10
Seizure	0	0	0	0	0	0	N/A
NICU admission > 48 h for full-term infant	2	1.8	0	0	0	0	N/A
Neonatal death	0	0	0	0	0	0	N/A
Composite adverse neonatal outcome	17	15.6	94	32.0	21	50.0	0.001[a]

Abbreviations: N/A, not available; NICU, neonatal intensive care unit; PE, preeclampsia..
[a]Significant difference in all multiple comparisons between the PE groups.
[b]Fisher's exact tests were used when several cells have expected counts less than 5.

increased liver enzymes, neurological symptoms, admission to intensive care unit, eclampsia, cesarean delivery, preterm birth, and low birth weight.[23,24] One of these studies showed that high maternal UP/CR was also associated with low Apgar scores and perinatal death.[23] Recent multicenter prospective studies conducted in low- and middle-income countries have developed and validated clinical prediction models for adverse maternal outcomes and perinatal death among pregnancies with hypertensive disorders (miniPIERS [Preeclampsia Integrated Estimate of Risk]). In those studies, dipstick proteinuria was included in the models as one of the predictors for these adverse outcomes.[28,29]

Conversely, other evidence does not support the association between proteinuria and adverse pregnancy outcomes.[15–20] The most comprehensive study is a systematic review of 16 primary studies conducted in 2009.[18] This systematic review showed that proteinuria was not associated with eclampsia, abruption, or HELLP syndrome, neonatal death, perinatal death, SGA, or NICU admission. Only the stillbirth rate was found to be higher in pregnancies with heavy proteinuria (positive likelihood ratio, 2.0; 95% confidence interval, 1.5–2.7). That systematic review, however, did not report associations with other important adverse outcomes such as preterm birth rate and neonatal morbidity. Importantly, 5 of the 16 studies (31.2%) were retrospective and proteinuria quantification was performed by dipstick also in 5 studies. Other limitations included heterogeneity among the studies in regard to study population, definition of PE, and proteinuria thresholds.

One retrospective cohort included in the systematic review had a similar design to our study.[15] Perinatal outcomes were compared between preeclamptic pregnancies with 24-hour proteinuria < 5, 5 to 9.9, and ≥ 10 g. This study reported that maternal outcomes did not differ between the PE subgroups. The authors found that compared with women with the lesser amounts of proteinuria (< 5 g/24 hours), those women with ≥ 10 g proteinuria were diagnosed earlier (30.6 ± 3.3 vs. 32.3 ± 3.4 weeks) and had earlier deliveries (30.9 ± 3.3 vs. 33.0 ± 3.2 weeks). Neonatal complications, that is, RDS and IVH were more common in infants born to mothers with ≥ 10 g/24 hours of proteinuria compared with the other subsets of patients, but the difference was not statistically different.

Clinical management of enrolled patients was dictated by institutional standardized protocols of participating centers and the final decision for delivery was made considering the global maternal and fetal condition. Composite adverse maternal outcome occurred in the range of 3 to 6% of all pregnancies and it was similar across the PE groups. Adherence to clinical protocols including prompt delivery in tertiary centers likely explains the low rate of serious adverse maternal outcomes, stillbirth, and neonatal mortality in this cohort. Massive UP excretion > 2.7 g in 12 hours or > 5 g in 24 hours was highly prevalent in pregnancies with early onset of PE < 34 weeks, a variety of PE typically associated with the greatest maternal and perinatal risk. Current clinical obstetrical guidelines in the United States and Canada recommend the exclusion of massive proteinuria > 5 g/24 hours[14,30] as a marker of clinical severity and delivery $< 37^{0/7}$ weeks is not indicated if this is the only detected abnormality. This may be reasonable if massive proteinuria is an isolated finding; however, it is frequently associated with other clinical manifestations and laboratory abnormalities indicative of greater disease severity and a higher rate of specific adverse pregnancy outcomes.

Exclusion of massive proteinuria from the diagnostic criteria of severe PE could erroneously lead clinicians to believe that these pregnancies have a low rate of complications and better outcomes than those now categorized as PE with "severe features."[14,30] In fact, our subgroup of nonproteinuria PE defined by current ACOG clinical and laboratory parameters as having severe features had the most favorable pregnancy outcomes among the studied groups. The median GA at delivery in this group was more than 4 weeks later than in the massive-proteinuria PE group, the mean birth weight was significantly higher, and the rates of cesarean delivery and neonatal complications were much lower. Although no longer part of the clinical criteria for diagnosis, our investigation supports assessment for and observatory vigilance of pregnancies with massive proteinuria. In deciding to undertake expectant management for these pregnancies, the clinician should closely follow a clinical protocol such as the one outlined in the committee opinion of the Society for Maternal-Fetal Medicine.[31]

Our data emphasize the limitations of current and past classifications of PE. The complexity of the disease makes it very challenging to categorize as less or more severe in the ample clinical spectrum. Until we develop a more accurate ancillary test that improves our ability to diagnose PE and predict its outcomes, we should not overlook pregnancies with massive proteinuria even if it is no longer considered a component of the diagnostic criteria for severe PE.

The small sample size of the massive-proteinuria PE group is a major limitation of our study. In the original cohort, proteinuria was measured by different methods including urine dipstick, UP/CR, and timed 12 and 24 hours urine collections. Although all possess accuracy limitations, the latter has been considered the "gold standard" test for several decades. Several studies have reported that the amount of proteinuria collected in a shorter period of time (12 hours) correlates well with the standard 24 hours urine collection.[26,27] We selected these two methods, as they were considered the most accurate tests available for the quantification of proteinuria. Unfortunately, only 406 of the 675 women diagnosed with PE underwent either of these tests. Our small sample size increases the probability of type II error in some of our statistical analysis. This is particularly true for the relatively rare but life-threatening maternal complications of PE. Also, the small number of cases with massive proteinuria limits our ability to perform additional analysis that might identify a proteinuria threshold at which adverse pregnancy outcomes could become significantly more likely. Although, an independent panel of experts made the diagnosis of PE using current clinical guidelines in the United States, we cannot exclude the possibility of selection bias in this cohort. Relevant clinical data such as

fetal testing results prior to delivery were not available for analysis limiting our capacity for explaining the high rate of preterm birth, cesarean delivery, and high frequency of low Apgar score in the massive-proteinuria PE group. Furthermore, umbilical cord gasses were only obtained in approximately half of the neonates.

In summary, our investigation found that massive proteinuria occurs frequently in preeclamptic pregnancies diagnosed at early GAs and is often associated with more severe maternal and laboratory abnormalities. We believe that quantification of maternal proteinuria by some method should continue to be part of the clinical evaluation of PE. Importantly, massive proteinuria is unlikely to be an isolated finding. When present, a judicious clinical assessment for the presence of other severe clinical features is justified. While some may argue that quantification of proteinuria is an insufficient predictor of severity and may have resulted in unnecessary early preterm birth, we believe this is unlikely. This cohort demonstrates the association of massive proteinuria with earlier disease onset, severe BP elevations, more frequent laboratory abnormalities, severe maternal symptoms, low Apgar scores, and a higher cesarean delivery rate suggesting that it is a covariable indicating maternal/fetal severity rather than a confounding variable. We encourage the clinician to consider the implications that massive proteinuria has in the clinical course and outcome of PE.

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